REMARKS

These remarks are in response to the Office Action mailed January 8, 2009. Claims 1-10, 19, 58 and 60 have been cancelled without prejudice to Applicants' right to prosecute the cancelled subject matter in any divisional, continuation, continuation-in-part or other application.

Applicants respectfully thank Examiner Dunston for the courteous telephonic interview conducted with Applicants' representative, Joseph R. Baker, on January 28, 2009. During the Interview amendments and remarks were considered to overcome the pending rejections. Examiner Dunston suggested amending claim 49 to clarify that the controls relate to the same biomarkers and sample location.

Applicants respectfully submit that the Examiner in charge of this application has changed three times in the past 3 years and that consistency with a single Examiner would greatly advance prosecution and consideration of amendments and remarks in the present matter. Applicants kindly request that the Examiner contact the undersigned by telephone should there be any opportunity to advance prosecution of the present case.

Claim 49 has been amended as suggested by the Examiner. Furthermore, claim 49 has been amended to indicate that the analysis can be performed by MANOVA as a measure of a difference. Support for the amendment can be found, for example, at paragraphs [0009], [0024] and [0028] of U.S. Patent Publication No. 20050014165 (corresponding to the present application).

Claims 98-107 have been added. Support for the new claims can be found throughout the specification and claims as originally filed (see, e.g., claims 49-59 as originally filed).

No new matter is believed to have been introduced.

I. CLAIM OBJECTIONS

Claims 52, 53, 60, 96 and 97 stand objected to for various phrasing, grammar and dependent format. Claims 60 has been cancelled, thus the objection is moot with respect to this claim. Claim 52, 53, 96 and 97 are objected to for a lack of consistent phrasing with the parent claims. Claims 52, 53, 96 and 97 have been

amended to maintain consistency. Accordingly, the claim objections may be withdrawn.

II. NON-STATUTORY DOUBLE PATENTING REJECTION

Claims 49-51-53, 60-61, 63 and 64 stand provisionally rejected on the grounds of non-statutory obviousness-type double patenting in view of copending application no. 12/180,347. Applicants respectfully traverse this rejection.

Because an obviousness-type double patenting rejection is ultimately based upon the claims, Applicants cannot properly address the rejection without an indication of allowable subject matter in one or both cases. Accordingly, Applicants respectfully request that this rejection be held in abeyance.

Claims 49, 54 and 60-62 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly unpatenable over claims 104-107 of copending application no. 11/827,894. Applicants submit herewith a Terminal Disclaimer. Thus, this rejection may be properly withdrawn.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 49, 51-55, 57-58, 60-64, 79, 81-88 and 96-97 stand rejected under 35 U.S.C. §112, first paragraph, because, while being enabling for (A) a method for assessing the risk of colorectal polyps and colorectal cancer in a subject, comprising (i) obtaining a biological colorectal sample from the subject; (ii) isolating cellular RNA from the sample; (iii) amplifying and quantifying RNA expression levels for SEQ ID NO:s 1 ad 2; (iv) comparing the quantified expression levels of SEQ ID NOs: 1 And 2 in normal control colorectal samples; and (v) determining an increased risk of colorectal polyps and colorectal cancer in the subject when at least one of SEQ ID NOs: 1 and 2 is increased in expression in the sample from the subject as compared to the normal control; and (B) A kit for assessing the risk of colorectal polyps and colorectal cancer, comprising oligonucleotides comprising the sequences set forth in SEQ ID NOs: 45, 46, 47 and 48, allegedly does not provide enablement for using the method for determination of colorectal polyps and colorectal cancer (i.e., diagnosis), or management of colorectal polyps and colorectal cancer, which includes estimating

risk, early diagnosis, establishing prognosis, monitoring patient treatment or detecting relapse; using any normal control sample as a comparison; using any change in expression levels to determine risk; using biomarkers selected form SEQ ID NOs: 5, 15, and 16. The rejection is moot with respect to claims 58 and 60. Applicants respectfully traverse this rejection.

New claim 98 sets forth the subject matter indicated as enabled above. Claims depending from claim 98 are further enabled by the specification and are readily practiced using the specification as a guide along with knowledge of one of ordinary skill in the art. Accordingly, Applicants submit that claims 98-107 are allowable, particularly in view of the Examiner statement related to enabled subject matter.

Claim 49 has been amended consistent with the Examiner's indication that the disclosure is enabled for "risk assessment". Thus, Applicants believe that the "management" of a subject following risk assessment is properly set forth and enabled in the claims.

Attached hereto as exhibits A and B are references that further demonstrate the methods and enablement of the disclosure. The references are not prior art to the present application, but are provided as further proof of principle.

Turning first to Exhibit A (Lu et al.) the reference demonstrates that further analysis and collection effort using the same and original panel of biomarkers was capable of identifying subjects with polyps or colorectal cancer. A brief summary of the data is depicted in Table 5 on page 721 of Exhibit A. Table 5 (reproduced below), indicates, for example, that 21 out of 25 subjects with polyps had altered gene expression compared to control subjects when using a minimally-invasive method (e.g., a swab) and 20 out of 25 subjects demonstrated altered gene expression compared to control using a biopsy method. In other words using a panel of biomarkers of the disclosure, a subject having or at risk of having polyps could be identified more than 80% of the time.

TABLE 5. Summary of patients with altered gene expression in three groups vs. control group

	Number of patients with altered gene expression	
Groups	*Swab samples (%)*	*Biopsy samples (%)*
FH/SH (n = 37)	26/37 (70)	25/37 (68)
Polyps (n = 25)	21/25 (84)	20/25 (80)
Cancer (n = 12)	12/12 (100)	NA

FH/SH, family or self-reported history; NA, not applicable.

Accordingly, the methods of the disclosure are useful for determining and assessing a polyp or a risk of polyps or a cancer or a risk of cancer contrary to the lack of enablement rejection indicated above.

Furthermore, in the second column of page 721, second full paragraph, the reference states, "Each individual in the cancer group exhibited alterations of multiple genes, up to 14 in one case. COX2 [SEQ ID NO:2], interleukin-8 [SEQ ID NO:1] and CXCR2 [SEQ ID NO:3] were among the more prevalent genes to be altered in the polyps and the FH/SH groups."

The Office Action indicates, for example, at page 19, last paragraph, that "the art cited above clearly evidences that establishing expression of any single gene in any give cell system as a valid biomarker for any give condition is highly unpredicatable. . ." However, Applicants respectfully direct the Examiner to Exhibit B (Rubie et al.) which indicates IL-8 is a biomarker that is highly/overly expressed in all stages of colorectal cancer. This is in sharp contradiction to the references cited in the Office Action. For example, Rubie et al. state, "IL-8 mRNA [SEQ ID NO:1] and protein expression was significantly up-regulated in all pathological colorectal entities investigated, compared with the corresponding neighboring tissues." (see, e.g., Abstract, "Results"). In addition, Exhibit B also indicates that IL-8 would be useful as a prognostic and diagnostic indicator (see, e.g., first column page 5001 of Exhibit B).

The Office Action further indicates that it is unclear how the quantification of the biomarkers of the disclosure would predict or diagnose (e.g. what measurement relative to a control) would be indicative of a change. Applicants have amended claim 49 to indicate the measurements can be analyzed using a MANOVA statistical

technique to indicate a change compared to a control as indicative of colorectal cancer or polyps. Such statistical calculations are known in the art.

Applicants respectfully submit that they have provided both animal and human data demonstrating the methods of the invention along with after-arising publications demonstrating the further proof of principle of the disclosure. The data and references demonstrate that both a panel (Lu et al.) and a single marker (Rubie et al.) can provide information important for clinical practice/managmenet of patients or subjects. Furthermore, the data and references demonstrate that not only can the methods be useful for risk assessment and diagnosis of cancer, but also polyps.

Should the Examiner feel that any statement or remark above require further clarification, the Examiner is invited to call the undersigned. For at least the foregoing reasons, Applicants respectfully request withdrawal of this rejection.

IV. REJECTION UNDER 35 U.S.C. §103

Claims 79, 81-87 stand rejected under 35 U.S.C. §102 as allegedly anticipated by TaqMan® EZ RT-PCR kit. Applicants respectfully traverse this rejection.

Applicants have amended claim 79, upon which the remaining claims depend. Applicants respectfully submit that the cited references do not teach or suggest alone or in combination a kit comprising a normal colorectal amount of a biomarker and instructions for measuring the expression level for risk assessment. Accordingly, Applicants respectfully request withdrawal of the rejection.

For at least the foregoing, the Applicant submits that the claimed invention is patentable and request reconsideration and notice of such allowable subject matter.

The Director is authorized to charge any required fee or credit any overpayment to Deposit Account Number 50-4586, please reference the attorney docket number above.

The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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